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Review Article

Stroke as a Cause of TGA? Narrative Review and Hypothesis

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Abstract

The pathogenesis of transient global amnesia (TGA) remains unknown. Stroke has always been considered a possible cause because of the acute onset and focal nature of the condition. Whilst no evidence, clinical or neuroradiological, has been found to establish a diagnosis of stroke in the majority of TGA cases, occasional reports document radiological evidence of stroke. The purpose of this narrative review is to collate these disparate reports. These have presented TGA in association with lesions described as stroke, infarction or acute ischaemia in various locations related to Papez circuit: medial temporal lobe, hippocampus, fornix, thalamus, cingulate gyrus or bundle, striatum (caudate and putamen), corpus callosum, and frontal lobe. In light of these reports, a tentative hypothesis of TGA pathogenesis is suggested.

ABBREVIATIONS

CT: Computed Tomography; **DWI:** Diffusion-Weighted Imaging; **EHPDL:** Extra-Hippocampal Punctate Diffusion Lesions; **HPDL:** Hippocampal Punctate Diffusion Lesions; **MR:** Magnetic Resonance; **TGA:** Transient Global Amnesia; **TIA:** Transient Ischaemic Attack; **SD:** Spreading Depolarization

INTRODUCTION

Transient global amnesia (TGA) was first reported as such by Miller Fisher and Raymond Adams, who presented a number of patients in 1958 and in 1964 [1,2], although similar cases had been previously described in the medical literature under different names, e.g. episode of confusion with amnesia [3], *ictus amnésique* [4]. Fisher and Adams noted that the "possibility that such an episode might have been the first evidence of an approaching stroke … was responsible for our seeing so many of these patients", although it was their tentative view that TGA was "a special type of focal cerebral seizure" [2]. In addition to stroke and seizure, a form of migraine has also been postulated as a possible explanation of TGA. It has also been suggested that TGA might be a symptom complex rather than a single specific disease entity [5].

The pathophysiology of TGA has remained uncertain since Fisher and Adams' descriptions. Transient ischaemic attack (TIA) and stroke are often considered in the differential diagnosis of TGA [6], perhaps not least because a stroke, most usually in the posterior circulation, may on occasion cause a pure, or relatively pure, amnesic syndrome [7-9]. The issue is of importance not only for immediate patient management but also for prognosis, since whether or not TGA is a risk factor for subsequent stroke remains unresolved [10].

The development of clinical diagnostic criteria for TGA, predating widespread availability of structural brain imaging, sought to exclude stroke as a cause by limiting the observed cognitive impairment to amnesia (i.e. no aphasia, apraxia), excluding focal neurological symptoms or signs during or after the attack, and specifying that attacks must resolve within 24 hours [11]. Nevertheless, when neuroimaging with computed tomography (CT) became increasingly available from the 1980s occasional TGA cases with changes indicative of established ischaemic stroke accompanying the typical clinical phenotype were reported [12-14].

Subsequently, magnetic resonance (MR) imaging studies of the brain in TGA using diffusion-weighted imaging (DWI) sequences have typically shown focal areas of high signal within the CA1 sector of the hippocampal formation. These changes may appear over a few days following the acute episode and then resolve, and hence are unlike the imaging findings in acute stroke [15,16]. These MR-DWI changes are not specific to TGA, as the pattern of diffusion changes has also been reported in hippocampal ischaemia, limbic encephalitis and status epilepticus [17,18], but they may be used in the appropriate clinical setting to support a clinical diagnosis of TGA [15].

As was the case with CT, the clinical phenotype of TGA with MR imaging findings deemed consistent with stroke has been reported on occasion, suggesting that stroke may on occasion be the cause of TGA. The objectives of this study were to review such reports of stroke-related TGA. In light of this review, a tentative hypothesis of TGA pathogenesis in the context of stroke is suggested.

METHODS

The PubMed database was searched using "transient global amnesia", "TGA", "stroke", "infarct", "infarction", and "acute ischaemia" as major MESH terms. Articles from 1966 to end of January 2022 were reviewed. In addition, potentially relevant articles identified from the reference lists of these initial papers

were reviewed, along with reports known to the author from previous reading, including meeting abstracts. Although the selection was based on some simple inclusion/exclusion criteria (confined to publications post-dating the suggested TGA clinical diagnostic criteria of 1990 [11]; with MR brain imaging) it does not claim to be a systematic review. Many cases may not have been reported in the literature.

RESULTS

The literature search identified 30 publications in which a patient or patients with transient amnesia with the typical phenotype of TGA conforming to suggested clinical diagnostic criteria [11] were reported to have MR imaging changes showing evidence of stroke, infarct, infarction, or acute ischaemia [19-48] (Table 1).

As will be seen, the evidence base essentially comprises case reports, small case series, and meeting abstracts, hence the lowest level in the hierarchy of clinical evidence. These publications included descriptions of TGA reported in association with MR changes located in the medial temporal lobe [20,23,28,36,47], hippocampus [24-26,29,32,36,39,41,44,46], fornix [33,37], thalamus [19,31,38], cingulate gyrus or bundle [30,43,45], striatum (caudate and putamen) [22,27,34,40,48], corpus callosum [21,35], and frontal lobe [42,44].

Other case series were few and lacked clinical detail, hence their non-inclusion. Michel et al. reported on 13 patients with ischaemic stroke in which the main presenting symptom was amnesia and in two of whom the presentation was reported to be indistinguishable from TGA but they did not specify lesion location in these two patients [9]. Eleftheriou et al. reported in abstract on 103 TGA cases of whom 43 underwent MR imaging, with changes of acute infarction seen in various locations (hippocampus,

Table 1: Reports of MR-confirmed acute ischaemia, infarction, or stroke associated with the clinical phenotype of TGA.

Location	Reference	Demographic and other clinical features	MR imaging findings
Temporal lobe:			
	Greer et al. (2001) [20]	F77	Left mesial temporal lobe ischaemic infarct
	López-Pesquera et al. (2005) [23]	F49	Tiny ischaemic stroke in white matter of left temporal lobe
	Graff-Radford et al. (2013) [28]	F56; following coiling of small posterior circulation cerebral aneurysm	Small medial temporal lobe strokes
	Duan et al. (2016) [36]	M72; coronary angiography	Acute infarction in left hippocampus and temporal lobe
	Ramanathan & Wachsman (2021) [47] (n = 2)	F48 history of hypertension, COVID-19 +ve F71 history of hypertension, COVID-19 +ve	Bilateral medial temporal lobe infarcts Small R temporal lobe infarct
Hippocampus:			
	Adler et al. (2012) [24]	F65	Subtle ischaemic region in the right hippocampus compatible with acute infarct
	Carota et al. (2012) [25]	R41; "TGA plus" (anomic pauses, "amnesic aphasia"); patent foramen ovale	Acute infarct, dorsal part of left hippocampal body
	Gungor-Tuncer et al. (2012) [26] and (2015) [32] (case 2)	F62; history of migraine	Left pons (7h); left hippocampal and right frontal areas (36h)
	Li and Hu (2013) [29]	M61	Bilateral hippocampal lesions, acute ischaemia
	Gungor-Tuncer et al. (2015) [32] (case 1)	F56; history of migraine	Two punctate acute infarcts in the left hippocampus
	Duan et al. (2016) [36] (n = 2)	M73; cerebral angiography, vertebral artery angioplasty M72; coronary angiography	Acute infarction in left hippocampus Acute infarction in left hippocampus and temporal lobe
	Naldi et al. (2017) [39]	F82	Right posterior hippocampal stroke
	Yun et al. (2017) [41]	M68	Bilateral hippocampal lesions
	Kang et al. (2021) [44]	M54	Right frontal and hippocampus strokes
	Sakihara et al. (2021) [46]	F35; septic embolus from infective endocarditis	Right hippocampus
Fornix:			
	Gupta et al. (2015) [33]	F66; paroxysmal atrial fibrillation	Body and left column of fornix infarction

	Meyer (2016) [37]	N/A	Left fornix infarction
Thalamus:			
	Pradalier et al. (2000) [19]	F54; history of migraine without aura	Right antero-inferior thalamic ischaemic lesion
	Giannantoni et al. (2015) [31]	F69	Thalamic ischaemic lesion
	Dogan et al. (2017) [38]	F65	Left thalamus and left paramedian mesencephalon infarcts
Cingulate gyrus:			
	Gallardo-Tur et al. (2014) [30]	M62; two TGA episodes	Acute ischemic stroke of small size (15 mm maximal diameter) at right cingulate gyrus
	Chau and Liu (2019) [43]	F60	Left cingulate gyrus
	Meng et al. (2021) [45]	F89; history of hypertension	L retrosplenial infarct (cingulate bundle and retrosplenial cortex)
Striatum (caudate, putamen):			
	Ravindran et al. (2004) [22]	M56	Acute ischemia in the body of right caudate nucleus
	Kim et al. (2012) [27]	F63	L putamen acute microinfarct
	Koltermann et al. (2015) [34]	M50	Acute ischaemic lacunar infarction, head of caudate nucleus
	Yoshida (2017) [40]	F67	Lacunar infarction of the left putamen
	Tarazona et al. (2021) [48]	F89; history of migraine	R lenticular nucleus (outermost putamen)
Corpus callosum:			
	Saito et al. (2003) [21]	M58	Small lesion of high signal intensity in the left retrosplenium of the corpus callosum
	Beyrouti et al. (2016) [35]	M62	Infarction of genu and body of corpus callosum
Frontal lobe:			
	Kim et al. (2018) [42] (n = 3)	No details	1. Left orbitofrontal. 2. Left prefrontal. 3. Right frontal and left parietal.
	Kang et al. (2021) [44]	M54	Right frontal and hippocampus strokes

temporal lobe, frontal lobe, post central gyrus) in 8 patients [49], hence essentially confirming the stroke localizations noted in the case reports. Ganeshan et al., found acute MR-DWI lesions with ADC hypointensity in 14/126 patients with clinically typical TGA (11%) and no other symptoms, hence clinically silent lesions. Of these, 8 were in the anterior circulation, 1 in the posterior circulation, 3 were in both anterior and posterior circulation; 2 were in subcortical posterior circulation locations. All of these 14 patients also had typical hippocampal CA1 MR-DWI changes [50]. The patient described by Mariaca et al., appears to have had two incidental (clinically silent) right parietal lesions associated with high grade right middle cerebral artery stenosis along with the typical clinical and MR-DWI changes of TGA [51].

DISCUSSION & CONCLUSION

The data identified by this review were limited to case reports and case series not exceeding single figures. It is likely that case underascertainment and under reporting contributed to the scarcity of evidence. Nevertheless, the data suggest that neuroradiological changes suggesting stroke, infarct or infarction, or acute ischaemia, occurring in the hippocampus or in structures linked to the hippocampal formation, may on occasion manifest with the typical clinical phenotype of TGA.

Some caution is, however, required before accepting all of these cases at face value.

In many, imaging findings of diffusion restriction seem to have been equated with stroke, infarction, or acute ischaemia without follow-up imaging to exclude the possibility that the visualized changes were merely transient, as is the case for MR-DWI CA1 punctate lesions in TGA [15,16] (some publications did indeed show that the reported imaging changes were transient, and hence perhaps simply the typical changes of TGA [29]). It is known that conditions other than TGA can cause punctate MR-DWI changes in the hippocampus [17] and such changes have also been reported in asymptomatic individuals [52]. Furthermore, the MR-DWI appearances in TGA and hippocampal infarct may be radiologically indistinguishable, the differentiation relying on clinical features [18]. Accordingly, it may be best to label such radiological changes descriptively, for example as hippocampal or extra-hippocampal punctate diffusion lesions (HPDL, EHPDL), rather than ascribe a pathological cause (stroke, infarction, acute ischaemia) without adequate clinical or radiological evidence. This reformulation acknowledges that the imaging appearances indicate metabolically stressed tissue, leading to diffusion restriction, but remains agnostic as to the cause of this restriction pending further information. They may possibly be equivalent to the changes typically seen in CA1, but occurring in other locations.

If, despite these caveats, it is accepted that at least some of these reports do indeed present examples of stroke-related TGA, how are these cases to be interpreted? Are they simply examples of chance concurrence? Or might they be telling us something about TGA pathophysiology? The pathogenic mechanisms of TGA have not been fully characterized. More than 35 years ago Olesen and Jorgensen suggested that the spreading depression of Leão, a mechanism previously implicated in migraine aura, was "theoretically … a very likely pathogenetic mechanism of TGA" [53], a view which still persists [54,55]. Spreading depression is now often characterized as part of a continuum with spreading depolarization (SD), a wave of electrophysiological hyperactivity followed by a wave of inhibition which propagates across the cerebral cortex at around 1-10 mm/min. SD is thought to disrupt neuronal electrical activity, mediated through changes in extracellular ion concentrations and toxic release of glutamate. SD has been implicated in various disease processes besides migraine aura and TGA, including traumatic brain injury, epileptic seizures and sudden unexplained death in epilepsy, and also brain ischaemia [56,57].

The paucity of the data necessarily makes any interpretation of results tentative, pending higher levels of evidence from systematic studies. Nevertheless, the involvement of memory eloquent brain structures, linked through Papez circuit, in many of the reported cases of stroke-related TGA, as well as frontal lobe structures involved in the organization and monitoring of memory processes, and the absence of significant hemisphere strokes, is sufficient to give pause for thought. A parsimonious hypothesis would therefore be that an acute event, ischaemic or otherwise, may trigger SD, which could lead to an episode of TGA. SD does not respect arterial boundaries, and hence acute strokes in various locations might initiate TGA if SD propagated to reach memory eloquent structures. There is preliminary evidence for a spatial hierarchy of susceptibility to SD within the brain (occipital > parietal > frontal > middle temporal) [58], which might in part explain the rarity of stroke-related TGA, as medial temporal lobe structures are the least susceptible to sustain and propagate SD.

Stroke-related TGA might therefore be regarded as a symptomatic (or secondary) form of TGA, rather than the more usually encountered idiopathic (or primary) form. Other processes involving the cerebral vasculature which have also on occasion been associated with episodes of TGA, and which might therefore also be relevant to these considerations, include cerebral angiography (as in some of these stroke-related cases [28,36]), reversible cerebrovascular vasoconstriction syndrome, CADASIL, and subarachnoid haemorrhage. TGA may also occur on occasion before a typical migraine headache, prompting a view that it may be a form of migraine aura, which itself may sometimes be the sole clinical manifestation of ischaemic stroke [59]. SD has been suggested as a possible explanation for migrainous infarction [60,61]. SD may therefore be a unifying hypothesis for TGA pathogenesis, irrespective of whether it is associated with stroke, migraine, or even seizure. The testability of this hypothesis will depend upon the development of methods to monitor SD *in vivo.*

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